REMARKS/ARGUMENTS

Claims 1, 4-35 and 45-47 are pending. Claim 45 has been canceled without prejudice and without acquiescence. Claims 1, 6, 20, and 45-47 have been amended without prejudice and without acquiescence to clearly define the invention claimed. Claims 1 and 6 have been amended without prejudice and without acquiescence to clearly provide the identity of the entire cysteine protease. The amendments submitted herein do not add any new matter. Support for the amendments appears on page 7, lines 6-8 and examples 6-20 (pages 22-35).

The issues outstanding in this application are as follows:

- The disclosure has been objected to due to an informality on Page 18 referring to "coinecticut".

- Claim 45 has been objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1.

- Claims 1, 4-35, 45-47 have been rejected under 35 U.S.C. § 112 first paragraph as allegedly lacking adequate written description.

- Claims 1, 4-35, 45-47 have been rejected under 35 U.S.C. § 112 second paragraph as being indefinite.

I. Specification

The Examiner has objected to the Specification as containing informalities. Applications respectfully traverse.

In order to advance prosecution of this application, Applicants have amended the alleged informality on page 18. In light of this amendment, Applicants request that the objection be withdrawn.

II. Claim Objection

The Examiner has objected to the claim 45 under 37 CFR 1.75 as being a substantial duplicate of claim 1. Applications respectfully traverse.

In order to advance prosecution of this application, Applicants have canceled without prejudice and without acquiescence claim 45. In light of this amendment, Applicants request that the objection be withdrawn.

III. Claims 1, 4-35, 45-47 are supported by the written description.

Examiner has rejected claims 1, 4-35, 45-47 due to a lack of adequate written description. The Examiner asserts that the instant specification fails to provide the identity of the entire cysteine protease, and that the full reference sequence from which specific amino acid substitutions are drawn is required for the written description to be commensurate in scope with the claims drawn to specific amino acid substitutions. The Examiner also asserts that failing to provide a precise description of the reference sequence would not allow a person skilled in the art to recognize that the inventor invented what is claimed. The Applicants respectfully traverse.

In the publication "A conserved *Streptococcus pyogenes* extracellular cysteine protease cleaves human fibronectin and degrades vitronectin" by Kapur et al., *Microbial Pathogenesis* Nov. 1993; 15: 327-346, the inventors reported the methodical sequencing of 39 SPEB alleles in 67 *S. pyogenes* strains and explicitly state that 33 of the 39 identified alleles differ in sequence from one another at only one or two amino acids that are clustered in a ten-amino acid region (amino acid positions 308-317). The nucleotide sequences that code for allelic variations within the identified ten-amino acid region are disclosed on page 331 (figure 3) of the cited volume of *Microbial Pathogenesis*. Furthermore, the figure legend corresponding to Figure 3 of the above-cited publication divulges the accession numbers assigned to the DNA sequences coding for the complete amino acid sequences of the SPEB protein and of the 33 highly conserved allelic variants thereof (EMBL/GenBank/DDBL accession numbers L26125-L26162). Therefore, the complete polynucleotide and amino acids structure of the SPEB protein used as a reference sequence to generate the invention of the instant claims was available to skilled artisans at the time of the instant application and is not required. To clarify any ambiguities to the claims resulting from Applicants use of the term "cysteine protease" and "streptococcal pyrogenic exotoxin B (SPEB)" interchangeably, Applicants have amended the language of the claims. Claims 1 and 6 are now drawn to immunological compositions cointaining a purified non-proteolytic streptococcal pyrogenic exotoxin B in lieu of a purified non-proteolytic cysteine protease.

Furthermore, the instant specification details the purification scheme used by the Applicants to purify *S. pyogenes* cysteine protease and *in vitro* and *in vivo* biochemical, functional and immunologic evidence to confirm that the material obtained from the

disclosed purification scheme is the purified cysteine protease whose derivatives will be used in an immunologic composition of current claim 1.

The biochemical, functional and immunological examples cited in the instant specification one pages 19 and Fig. 1; 21 and Fig. 3; 6 lines 19-28 and Fig. 10 are drawn from the instant specification, also disclosed in Kapur et al., *Microb Path*, 1993 and Kapur et al., *Proc. Natl. Acad. Sci.* 90: 7676-7680 (published August, 1993), are sufficient for one of ordinary skill in the art to recognize that the inventors were in possession of a cysteine protease (i.e. SPEB) from *S. pyogenes* that can be used in an immunological composition. Furthermore, a skilled artisan would recognize without undue experimentation that the Applicants were able to purify the cysteine protease variants of current claim 1 which contain one or more amino acid substitutions specifically engineered to disrupt enzymatic activity or alter immunogenicity.

The disclosure, as instantly filed, follows C(2) written description criteria set out in Chisum § 7.04[1][c] 7-176 ¶5 as follows: "If the complete structure is not disclosed, determine whether the specification discloses other relevant identifying characteristics, i.e. physical and/or chemical characteristics and/or functional characteristics coupled with a known or disclosed correlation between function and structure, sufficient to describe the claimed invention in such full, clear concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. Disclosure of any combination of such identifying characteristics that would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. In such a case, a rejection for lack of written description under 35 U.S.C. §112 ¶ 1 must not be made".

The currently amended claim 1 is drawn to an immunological composition comprising a physiologically acceptable non-toxic vehicle containing a purified non-proteolytic SPEB, which produces an immune response in a mammal against Group A streptococcal infection, wherein said SPEB comprises at least one amino acid substitution and said amino acid substitution occurs at the amino acid position selected from the group consisting of Lys145, Gln185, Cys192, His340, Asn356 and Trp357.

The Examiner asserts that one skilled in the art would not have viewed the teachings of the specification sufficient to show that Applicants were in possession of an immunogenic

composition comprising the mutated cysteine protease or SPEB and method of producing an immune response as asserted in the specification as instantly claimed. The Applicants respectfully traverse.

A detailed description of the method used by the inventors to amplify the *speB* gene and its flanking regions from *S. pyogenes* chromosomal DNA using a polymerase chain reaction (PCR) strategy is disclosed on pages 22 and 23 of the instant specification. The specific primer sequences used to amplify the *speB* gene are disclosed on page 55, lines 15 and 16 of the instant specification. Additionally, page 22, lines 18-21 discloses the sequences of internal primers used by the inventors to sequence the complete *speB* gene. PCR and DNA sequencing are highly developed arts at the time of the instant application and the written description would allow a person of ordinary skill in art to recognize that **the inventors had knowledge of the DNA sequence** of the *speB* gene that would be required to perform the site-directed and random mutagenesis protocols disclosed in the instant specifications. *Emory University v. Glaxo Wellcome, Inc.*, 44 USPQ 2d 1407 states that "to meet the requirement of §112, the patent application need not utilize any particular form of disclosure. Instead 'the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed'". *In re Alton*, 76 F.3d 1168, 1172 states that "The adequate written description requirement, ...serves 'to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material'".

Applicants assert that the application on pages 32, line 16, describes the method for the creation of the genus of mutated cysteine proteases and a rationale for specifically mutating amino acids Lys145, Gln185, Cys192, His340, Asn356 and Trp357 into structurally neutral alanines. Applicants assert that the numbering system for protein is consistent and one of skill in the art is aware of the position of amino acids. Thus, one of skill in the art is capable of determining amino acids at positions 145, 185, etc. Furthermore, both site-directed and random mutagenesis techniques are described in the application. Figure 8 describes the specific amino acid substitutions at positions 145, 185, 192, 340, 356, and 357, referred to in the specification on page 32, line 20. On page 32, line 16, the rationale and mutagenesis scheme is described in such a way as to create mutants which "(i) disrupt protease activity; (ii) prevent zymogen processing; (iii) prevent substrate binding; and (iv) alter immunoreactivity."

Site-directed mutagenesis was a well-developed art at the time the application was filed. Applicants assert that the instant specification adequately conveys to a person of ordinary skill in the art that the inventors had knowledge of the SPEB DNA and amino acid sequences. Applicants also assert that methods and procedures described in the instant specification would allow the inventors to mutate amino acids 145, 185, 192, 340, 356 and 357 into alanines. The teachings of the instant specification would allow a skilled artisan to recognize that the inventors were able to purify recombinant wild-type (including known allelic variants) or engineered cysteine proteases (SPEB) from *S. pyogenes* that express a gene encoding a non-proteolytic cysteine protease containing mutations at the amino acids Lys145, Gln185, Cys192, His340, Asn356 and Trp357, or genes including two or more mutations at amino acids Lys145, Gln185, Cys192, His340, Asn356 and Trp357 without undue experimentation. *In re Alton*, 76 F.3d 1168, 1175 states that "If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, **even if every nuance of the claims is not explicitly described in the specification** then the adequate written description requirement is met" [emphasis added].

The recombinant proteins containing said amino acid substitutions would have then been easily purified using the purification procedure described in the instant specification and incorporated into an immunological composition comprising a physiologically acceptable non-toxic vehicle containing a purified non-proteolytic SPEB, which produces an immune response in a mammal against Group A streptococcal infection, wherein said SPEB comprises at least one amino acid substitution and said amino acid substitution occurs at the amino acid position selected from the group consisting of Lys145, Gln185, Cys192, His340, Asn356 and Trp357. Therefore, the Applicants assert that disclosure of the entire cysteine protease (SPEB) reference sequence is not required to allow a person of ordinary skill in the art to recognize that the inventors were in possession of the claimed invention at the time of the instant application. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996) states that "*ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question"

In light of the above arguments, Applicants believe that the written description is commensurate in scope with the claims drawn to specific amino acid substitutions. The

Applicants therefore respectfully request withdrawal of 35 U.S.C. § 112 written description rejection of claims 1, 4-35 and 46-47.

II Claims 1, 4-35, 46-47 are definite

The Examiner rejects claims 1, 4-35, 45-47 under 35 U.S.C. 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner asserts that acronyms like Lys145, Gln185, Cys196, His340, Asn36 and Trp357 must be spelled out when used for the first time in a chain of letters. The Applicants respectfully traverse.

The three-letter amino acid abbreviations presented in claims 1, 4-35, 45-47 conform to the format required by WIPO Standard ST.25 (1998) Appendix 2, Table 3 (incorporated by reference in 37 CFR 1.821) and are not acronyms. However, in order to expedite the prosecution of this patent, the Applicants have amended claims 1, 4-35 and 46-47 without prejudice and without acquiescence. Claims 1, 4-35, 46 and 47 have been amended according to the wishes of the Examiner. Amino acid sequence have been spelled out in full before using three-letter amino acid abbreviations in subsequent claims.

CONCLUSION

Claims 1, 4-35, 46 and 47 are pending in this application. Claim 45 has been withdrawn because it is a substantial overlap with claim 1. Applicants retain the right to file a divisional application to any cancelled or withdrawn claims.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

If there are any outstanding issues, Applicants request that the Examiner contact the undersigned for a quick resolution.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P00965US0 from which the undersigned is authorized to draw.

Dated: May 9, 2003

Respectfully submitted,

By _____
Melissa W. Acosta
Registration No.: 45,872
FULBRIGHT & JAWORSKI L.L.P.
1301 McKinney, Suite 5100
Houston, Texas 77010-3095
(713) 651-5151
(713) 651-5246 (Fax)